REMARKS

The Amendments

The claims are amended to incorporate the substance of claims 2, 15 and 20 into the independent claims. The claims are further amended to better conform them to U.S. practice. Also, the substance of claim 8 is incorporated into claim 7; see also Example 2 supporting this amendment. Support for the new claims is found in the specification as a whole, for example, the paragraph bridging pages 2-3; and, page 5, lines 11-16.

The amendments do not narrow the scope of the claims and/or were not made for reasons related to patentability. The amendments should not be interpreted as an acquiescence to any objection or rejection made in this application. To the extent that the amendments avoid the prior art, competitors are warned that the amendments are not intended to and do not limit the scope of equivalents which may be asserted on subject matter outside the literal scope of any patented claims but not anticipated or rendered obvious by the prior art. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application, which has been canceled by any of the above amendments.

The Restriction Requirement

The non-elected claims are canceled and will be pursued in a divisional application.

The Claim Objections and Rejection under 35 U.S.C. §112, second paragraph

The objection to claim 1 and the rejection of claims 2, 5, 6 13, 16 and 21 under 35 U.S.C. §112, second paragraph, are believed to be rendered moot in view of the claims as currently presented.

The Rejections under 35 U.S.C. §102

The rejections of claims 1, 3, 5, 7, 10-12 and 16-17 and of claims 18-20 under 35 U.S.C. §102 as being anticipated by Gast (WO 98/04267) are respectfully traversed.

It is believed that these rejections are rendered moot by the above amendments. Claims 2 and 15 were not subject to these rejections and the substance of those claims is now incorporated into independent claims 1 and 10 and, thus, claims 3-7, 9, 11-14 and 16-19 dependent thereon. Further, it is believed that claim 20 (now incorporated into independent claim 18) should not have been subject to the 35 U.S.C. §102 rejection since it recites the same language of claim 15 which was found distinct. In the 35 U.S.C. §103 rejection, the Examiner admitted that Gast did not disclose the use of drospirenone or ethinyl estradiol in micronized form. Accordingly, it would appear that claim 20 was not intended to be included in the 35 U.S.C. §102 rejection and, therefore, claim 18 (now incorporating the substance of claim 20) and claims dependent thereon should not be subject to the 35 U.S.C. §102 rejection. In any event, Gast does not disclose a composition or kit containing drospirenone or ethinyl estradiol in "micronized form or sprayed from a solution onto particles of an inert carrier." Thus, Gast cannot anticipate any of the instant claims.

For the above reasons, it is urged that the 35 U.S.C. §102 rejections be withdrawn.

The Rejection under 35 U.S.C. §103

The rejections of claims 2-4, 8, 9 and 13-15 and of claims 21-22 under 35 U.S.C. §103 as being obvious over Gast (WO 98/04267) are respectfully traversed.

As discussed above, and admitted in the Office Action, Gast does not disclose compositions or kits wherein drospirenone and/or ethinyl estradiol are provided in "micronized form or sprayed from a solution onto particles of an inert carrier." As discussed

in the instant specification at page 4, line 1, to page 5, line 9; and, page 2, lines 20-24; for example, applicants have surprisingly found that when drospirenone is provided in micronized form or in a form sprayed from a solution onto particles of an inert carrier rapid dissolution of the compound is observed which allows for enhanced bioavailability of the drug. The higher bioavailability allows use of a lower dosage amount to provide the same active effect while lessening the incidence of unwanted side effects.

It is alleged in the Office Action that it would have been obvious to one of ordinary skill in the art to employ drospirenone or ethinyl estradiol in micronized form. But there is no support anywhere on the record to support such an assertion. Gast certainly teaches nothing about use of micronized forms or any reason to suggest why such would have been desired. In order to establish obviousness under 35 U.S.C. §103, the prior art must suggest to one of ordinary skill in the art the desirability of the necessary modification. See In re Laskowski, 10 USPQ2d 1397 (Fed. Cir. 1989); and, In re Geiger, 2 USPQ2d 1276 (Fed. Cir. 1987). The cited prior art indicates no such desirability. For this reason alone, it is urged that Gast does not render the claimed invention prima facie obvious to one of ordinary skill in the art and the 35 U.S.C. §103 rejection should be withdrawn.

Although unnecessary in the absence of a prima facie case of obviousness, applicants have further proof of the nonobviousness of the claimed invention based on unexpected advantages thereof.

First, one of ordinary skill in the art would have known that drospirenone has poor solubility and a lack of stability in aqueous solutions at various pH values. Drospirenone is known to be prone to isomeric conversion to a non-active form at low pH and is degraded by hydrolysis at high pH; see, e.g., page 4, lines 4-7, of the specification. This instability would direct one of ordinary skill in the art away from providing drospirenone in micronized form – rather than suggest desirability thereof – because micronizing it would be expected to

heighten the instability thereof. As proof of such expectation, applicants attach herewith Supplementary Data on dissolution and bioavailability *in vitro* of micronized and non-micronized drospirenone. (The data can be submitted in Declaration form, if necessary.) The data shown in Figures 1-3 confirms the expectation in the art that in a low pH environment, as would be found in the stomach, the micronized form of drospirenone dissolves more rapidly and thereby is converted to its inactive form more rapidly than the non-micronized form. Therefore, the expectation (see Figure 3) would be that when the drug reaches the intestinal tract there would be a higher bioavailability when the non-micronized form is used because not as much would have been converted to the inactive form by hydrolysis.

Surprisingly, however, applicants have discovered that tablets containing drospirenone in micronized form according to their invention provide excellent bioavailability *in vivo*. This advantageous result is demonstrated by Examples 4 and 5 of the specification, pages 13-15. Example 4 shows that, in comparison to an oral formulation containing twice the amounts of drospirenone and ethinylestradiol, the micronized tablets of applicants' invention still provided higher bioavailability of the both of the drugs during *in vivo* administration. Example 5 confirms the effectiveness of administration of micronized forms of applicants' invention and the tolerance of the patient thereto in *in vivo* testing. Such high bioavailability and effectiveness could not have been expected by one of ordinary skill in the art for the reasons discussed above. It is urged that these advantages therefore serve as further proof of the nonobviousness of applicants' invention.

For all of the above reasons, it is respectfully submitted that Gast, considered as a whole, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejections under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

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Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 2, 8, 15, 20 and 23-35 have been canceled without prejudice or disclaimer.

Claims 1, 3, 5-7, 9-14, 16-19, 21 and 22 have been amended to read as follows:

1. **(Amended)** A pharmaceutical composition comprising, as a first active agent, 6β,7β;15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, drospirenone, ~~(drospirenone)~~ in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17α-ethinylestradiol ~~(ethinylestradiol)~~ in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, said drospirenone being in micronized form or sprayed from a solution onto particles of an inert carrier.

3. **(Amended)** A composition according to claim 1, comprising the drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg~~, in particular about 3 mg~~.

5. **(Amended)** A composition according to claim 1, comprising the ethinylestradiol in an amount corresponding to a daily dosage of from about 0.015 mg to about 0.04 mg~~, in particular from about 0.02 mg to about 0.03 mg~~.

6. **(Amended)** A composition according to claim 1, comprising an amount of drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg~~, in particular comprising an amount of drospirenone corresponding to a daily dosage of about 3.0 mg and ethinylestradiol in an amount corresponding to a daily dosage of 0.03 mg~~.

7. **(Amended)** A composition according to claim 1 wherein the pharmaceutically acceptable carrier or excipient is selected so as to promote rapid dissolution of the first and second active agents, the dissolution being determined by applying the USP paddle method, the dissolution media being water at 37 °C and the stirring rate being 50 rpm, and wherein rapid dissolution means that at least 70% of the first and second active substances are dissolved within 30 minutes.

9. **(Amended)** A composition according to claim 7 ~~8~~, wherein at least 80% of the first and second active agents are ~~released~~ dissolved within 20 minutes ~~of administration thereof~~.

10. **(Amended)** A pharmaceutical ~~preparation~~ kit consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units ~~comprises~~ each comprise a combination of 6β,7β;15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, drospirenone, in an amount of from about 2 mg to about 4 mg and 17α-ethinylestradiol in an amount from about 0.01 to about 0.05 mg, said drospirenone and said 17α-ethinylestradiol being in micronized form or sprayed from a solution onto particles of an inert carrier.

11. **(Amended)** A ~~preparation~~ kit according to claim 10, which additionally comprises 7 or less daily dosage units containing no active agent intended for oral administration subsequent to the period of at least 21 consecutive days, the total number of daily dosage units being at least 28.

12. **(Amended)** A ~~preparation~~ kit according to claim ~~10~~ 11, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units containing no active agent is 7, 6, 5 or 4.

13. **(Amended)** A ~~preparation~~ kit according to claim 10, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 ~~such as 2-4, in particular 2 or 3, times 28~~.

14. **(Amended)** A ~~preparation~~ kit according to claim ~~13~~ 10, which ~~additionally~~ comprises a number of daily dosage units comprising the combination of drospirenone and ethinylestradiol ~~of~~ which is a multiple of 21, 22, 23 or 24, and additionally comprises a number of daily dosage units containing no active agent ~~of~~ which is the same multiple of 7, 6, 5 or 4.

16. **(Amended)** A ~~preparation~~ kit according to claim 10 wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg~~, in particular about 3 mg~~, and 17α-ethinylestradiol in an amount of from about 0.015 mg to about 0.04 mg~~, in particular from about 0.015 mg to about 0.03 mg~~.

17. **(Amended)** A ~~preparation~~ kit according to claim 10, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and 17α-ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

18. **(Amended)** A pharmaceutical ~~preparation~~ kit consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units ~~comprises~~ comprise a combination of 6β,7β;15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, drospirenone, in an amount of from about 2 mg to about 4 mg and 17α-ethinylestradiol in an amount from about 0.01 to about 0.05 mg, wherein said drospirenone and said 17α-ethinylestradiol are in micronized form or sprayed from a solution onto particles of an inert carrier, and wherein ~~7 or less~~ at least 1 but no more than 7 of said daily dosage units contain 17α-ethinylestradiol ~~alone~~ in an amount from about 0.01 to about 0.05 mg and contain no drospirenone.

19. **(Amended)** A ~~preparation~~ kit according to claim 18, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units comprising ethinylestradiol ~~alone~~ without drospirenone is 7, 6, 5 or 4.

21. **(Amended)** A ~~preparation~~ kit according to claim 18, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg~~, in particular about 3 mg~~, and 17α-ethinylestradiol in an amount of from about 0.015 mg to about 0.04 mg~~, in particular from about 0.02 mg to about 0.03 mg~~.

22. **(Amended)** A ~~preparation~~ kit according to claim 18, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and 17α-ethinylestradiol in an amount ~~corresponding to~~ of from about 0.015 to about 0.03 mg.